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Case Report

Reversible oral EBV related-lymphoma in a patient with myasthenia graves disease: a case report and review of the literature

Oral EBV associated lenfoma with azathioprine in a myastenia disease

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Abstract

Thiopurines are widely used for remission maintenance and recurrence prevention in Myasthenia Graves disease (MG). We report a case of a 78-year-old man with MG treated with azathioprine (AZA) for 3 years earlier and who developed an intraoral ulcerated lesion. The biopsy specimen revealed a lymphoma and after discontinuation of AZA therapy the ulcerated lesion showed complete regression at 8 weeks, and no subsequent treatment was required.

Keywords

Myasthenia Graves; Azathioprine; Oral Lesion

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Introduction

MG is an autoimmune neuromuscular junction disease that causes muscle weakness [1]. If immunosuppression is required for MG treatment, it is recommended that the use of AZA therapy is recommended as a priority [1]. AZA is converted to 6-thioguanine after absorption and then incorporated into the DNA of the regenerating cells including mucosal cells [2]. AZA has been classified as 'carcinogenic to humans' by the International Agency for Research on Cancer (IARC) [3]. Likewise, a prospective, open, observational study was done to evaluate the long-term adverse effects profile of AZA in 163 MG patients in a larger patient cohort that they did not detect any lymphoma during the follow-up period [4].

We report a case of oral EBV-positive Hodgkin Lymphoma with an MG patient treated with AZA for 3 years and the lesion regressed spontaneously after AZA therapy was stopped.

Case Report

A 78- year- old man with a 5-year history of MG, complained ofa painful ulcer in his mouth for the last two months. He wastreated with 4x1 pyridostigmine for 5 years and 2mg/kg/day AZA for 3 years. A 1x1 cm whitish ulcerated lesion was identified at the left inferior retromolar trigone (Figure 1). The extraoral examination found no enlargements of the regional lymph node. The lesion biopsy revealed a leukemia or lymphoma infiltration. His personal and family history were unremarkable, except a history of osteoporosis, treated with cholecalciferol. He was regularly seen by dentists and was using his prosthesis carefully for many years. He has never smoked and drunk alcohol.

Routine laboratory works up including erythrocyte sedimentation rate, levels of lactate dehydrogenase and C-reactive protein, and renal, liver function tests showed bisitopenia (WBC: 4.74 10^3/µL, Hb: 12 g/dL). Computed tomography scan of the chest, abdomen, and pelvis didn't reveal any pathologic findings. A peripheral blood smear showed marked leukocytosis consisting of medium to large atypical lymphoid cells (Figure 2). A biopsy material (0,4X0,3X0,3cm) appearing as an inflammated white soft tissue was examined via light microscope evaluation, revealed distinctive necrotic tissue with diffuse infiltration by a polymorphous cellular infiltrate consisting of small lymphoid cells, histiocytes, some eosinophils, a single layer of scattered large blastic cells with prominent eosinophilic nucleoli, as well as Reed Stenberg cells which were typical for Hodgkin Lymphoma (Figure 3 and Figure 4).

At immunohistochemistry, the large cells showed strong positivity for CD30 and CD20 "Cluster of Differentiation, CD". The morphology, architectural features, and immunohistochemical findings were consistent with the diagnosis of classic Hodgkin's Lymphoma (cHL). In blood tests, the number of EBV DNA copies < 150 copy/ml indicating a low positivity. In the context of this, the disease was diagnosed as cHL associated with iatrogenic immunosuppression because of the long-term use of the drug (Figure 5).

During the follow- up of the patient, after the discontinuation of AZA, the oral lesions disappeared in two months period. Afterward, the patient who had ulcerated lesion for 3 years has remained stable. Repeated EBV testing was negative. The patient was treated with pyridostigmine and intravenous immunoglobulin. This treatment was successful in controlling the symptoms without ulcer and myasthenic crisis.

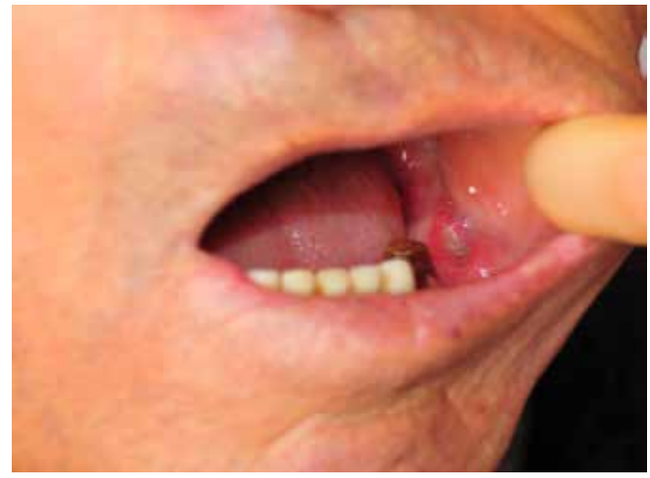

Figure 1. A 1x1 cm whitish ulcerated lesion was identified at the left inferior retromolar trigone.

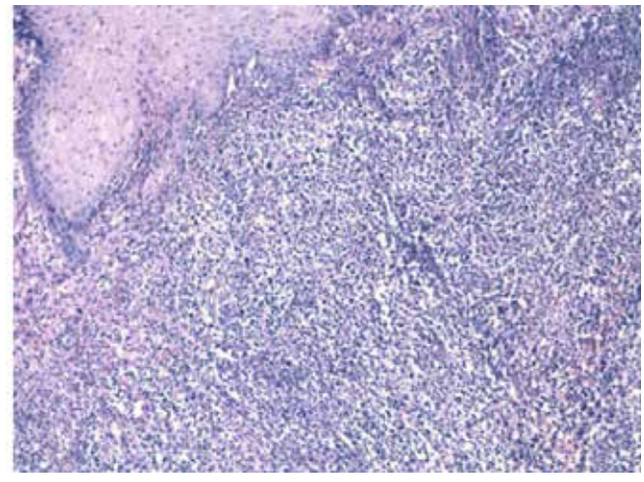

Figure 2. (1898-HE): lymphoid cells that infiltrate diffusely into the submucosa. In between, large transformed, multilobule nucleated cells are notable (H-E, x200)

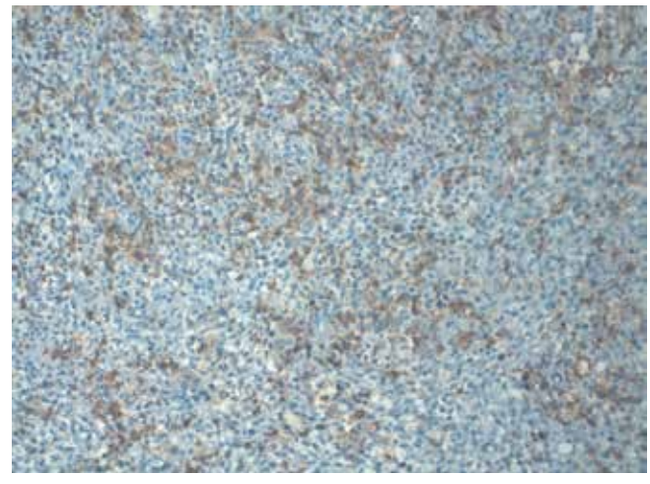

Figure 3. (1898-cd20): Immunophenotyping studies showed that CD20 positivity in large cells (Immunoperoxidase, x200)

Discussion

We describe a case of EBV-positive cHL in patients receiving therapy for MG with spontaneous regression after stopping of AZA. The patient presented with a well-circumscribed mucocutaneous ulcer in the mouth.

The complete involution of the lesion in a short time after discontinuation of AZA therapy indicates a pathogenetic role for AZA. Although the exact mechanism of action of 6-MP/AZA remains unknown, they do suppress the immune system, increas-

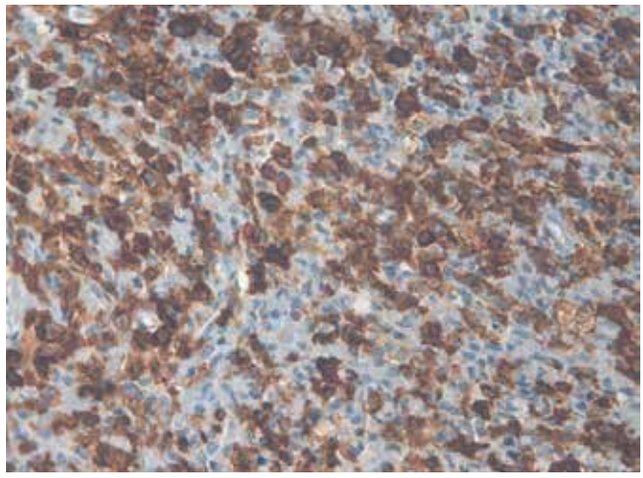

Figure 4. (1898-cd30): CD30 expression is observed diffusely in neoplastic cells (Immunoperoxidase, x400)

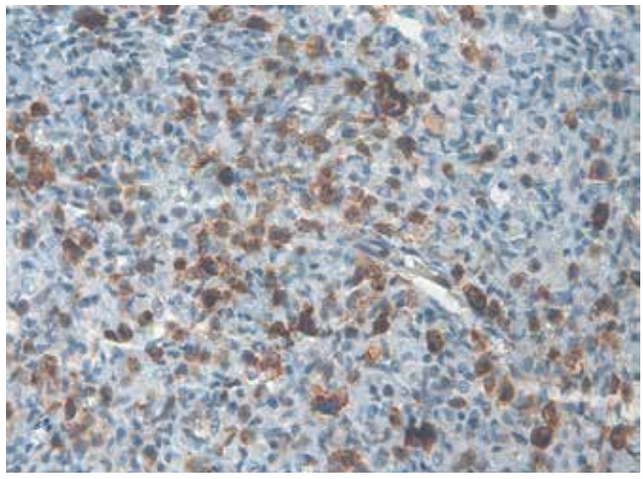

Figure 5. (1898-EBV): EBV-LMP1 is positive in large cells (Immunoperoxidase, x400)

ing the risks of infections and malignancies, precise pathogenesis may be related to the immunodulating effects of AZA. EBV-related lymphoproliferative disease (LPD) occurs most often in immunodeficient people [2]. Also, there have been reported similar cases associated with using immunosupressive therapy in the literature. There have been reported in cases that apparent spontaneous regression can be following the withdrawal of immunosuppressive therapy 1-3 months after the diagnosis. We want to attract attention to some points with this case. For example, this case has been seen in a short time with AZA therapy as three years. Another careful point is that spontaneous regression occured in a short time as 8 weeks after stopping AZA therapy.

The data on risk of cancer using AZA therapy for myasthenia are investigated in several studies. The further insight of this reseach has come from a large nationwide study in Denmark. According to this study, Pedersen et al. found that a high cumulative dose and long-term treatment with azathioprine was associated with a slightly increased risk of non-tobacco-related cancers, but not of tobacco-related cancers. However, the statistical precision was limited in the subcategory analyses. The results were similar in men and women for both time and dose of azathioprine MG [5].

Two other studies reported no increase in the risk of overall cancer with the use of azathioprine in patients by means of meaningful analyses of azathioprine use. All of the aforementioned studies included patients with MG with thymoma that were excluded in their study. They found that a high cumulative dose and long-term treatment (>10 years) with azathioprine may be associated with a small increase in the risk of overall cancer in patients with non-thymoma MG [6].

Evoli et al. have collected nationwide data since 1998. Their study has provided risk estimates of the effect of duration of immunosuppressive treatment on the risk of cancer in patients with MG. In that study, long duration (> 10 years) of AZA therapy increased the risk of cancer (OR: 2.2; 95% CI: 0.91– 5.72) [16]. Small numbers (n =18), however, prevented meaningful analyses of azathioprine use.

In addition, in the literature, there have been reported cases of spontaneous regression of malignancy following AZA therapy withdrawal in patients receiving therapy for autoimmune disease like MG.

The EBV-positive mucocutaneous ulcer was recently described as a clinicopathologic entity secondary to AZA therapy. According to some studies and cases which have been taken into consideration, age is an important factor. Usually, advanced age has facilitated to developing cancer in the immunocomproise patients and receiving immunosuppressive medication has accelerated to malign transformation. Age may be a confounding feature in the patients in whom EBV-lymphoma was linked to iatrogenic immunodeficiency. Notably, in a study by Docinov et al., they provided an analysis of 26 cases with a view to highlighting their clinicopathologic category, they provided discussion on the possible common pathogenetic mechanisms of EBV-induced ulcer in a different immunosuppressive setting including old age. Three patients had multiple episodes of oral mucosal ulceration with spontaneous resolution, others received chemotherapy, radiotherapy or combination therapy [7].

Conclusion

The case we described is unusual and to the best of our knowledge, an oral malignancy in an MG patient taking thiopurines is reported in the literature. In summary, the case highlights a patient with chronic immunosuppression secondary to azathioprine who developed EBV-positive mucocutaneous ulcer. The lesion involuted completely after discontinuation of azathioprine. The advanced age of the patient and the intake of immunosuppressive medications and EBV-positivity have contributed to improved lymphoma in our case. Further descriptions are required which prognosis of lymphoma in MG following treatment with thiopurines. Neurologist and other practitioners need to be aware of this complication of long-term medication-induced immunosuppression. The close follow-up of the patient beyond more frequent adverse effects should be paramount. In our opinion, any suspicious oral lesions should be referred for biopsy. As we have shown, oral malignancy, even in the absence of the classical risk factors, is possible.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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